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Patentanmeldung Nr. Patent application No. Demande de brevet n°

98122441.3

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Im Auftrag

For the President of the European Patent Office

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Anmeldung Nr.: Application no.: Demande n°: 98122441.3

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Bezeichnung der Erfindung: Title of the invention: Titre de l'invention:
Human semaphorin VIa (hsemaVIa) a novel gene involved in neuronal development and regeneration mechanisms during apoptosis, as a potential drug target structure

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Human semaphorin VIa (hsemaVIa), a novel gene involved in neuronal development and regeneration mechanisms during apoptosis, as a potential drug target structure

Specification

The present invention relates to human semaphorin VIa (hsemaVIa), a novel gene involved in neuronal development and regeneration mechanisms during apoptosis.

The invention comprises a nucleic acid coding for human semaphorin VIa comprising

(a) the nucleotide sequence shown in SEQ ID NO:1,

(b) a sequence corresponding to the nucleotide sequence shown in SEQ ID NO:1 within the degeneration of the genetic code, or

(c) a sequence which hybridizes with the sequences of (a) or/and (b) under stringent conditions.

The term "hybridization under stringent conditions" according to the present invention is used as described by Sambrook et al. (Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory Press (1989), 1.101-1.104). Preferably, a stringent hybridization according to the present invention is given when after washing for an hour with 1 x SSC and 0.1% SDS at 50°C, preferably at 55°C, more preferably at 62°C, and most preferably at 68°C, and more preferably for 1 hour with 0.2 x SSC and 0.1% SDS at 50°C, preferably at 55°C, more preferably at 62°C, and most preferably at 68°C a positive hybridization signal is still observed. A nucleotide sequence which hybridizes under such washing conditions with the nucleotide sequence shown in SEQ ID NO:1 or with a nucleotide sequence corresponding thereto within the degeneration of the genetic code is a nucleotide sequence according to the invention.

The nucleic acid according to the invention preferably is in operative association with an expression control sequence that is active in eukaroytic cells, preferably in mammal cells.

The nucleotide sequence according to the invention preferably is a DNA. However, it may also be an RNA or a nucleic acid analog, such as a peptidic nucleic acid.

The nucleic acid according to the invention preferably comprises a sequence having a homology of greater than 80%, preferably greater than 90%, and more preferably greater than 95% to the nucleotide sequence according to SEQ ID NO:1.

The invention further comprises a polypeptide encoded by a nucleic acid according to the invention.

The nucleic acids according to the invention can be obtained using known techniques, e.g. using short sections of the nucleotide sequence shown in SEQ ID NO:1 as hybridization probe or/and primer. They can, however, also be produced by chemical synthesis.

The invention further comprises a recombinant vector containing at least one copy of the nucleic acid according to the invention. This vector may be a prokaryotic or a eukaryotic vector which contains the nucleic acid according to the invention under the control of an expression signal (promoter, operator, enhancer etc.). Examples of prokaryotic vectors are chromosomal vectors such as bacteriophages and extra-chromosomal vectors such as plasmids, circulary plasmid vectors being particularly preferred. Prokaryotic vectors useful according to the present invention are, e.g., described in Sambrook et al., supra, chapter 1-4.

More preferably, the vector according to the invention is a eukaryotic vector, in particular a vector for mammal cells. Most preferred are vectors suitable for gene therapy, such as retrovirus, modified adenovirus or adeno-associated virus. Such vectors are known to the man skilled in the art of molecular biology and gene therapy and are also described in Sambrook et al., supra, chapter 16.

In addition to the polypeptide encoded by the nucleic acid of SEQ ID NO:1, the invention also relates to polypeptides differing therefrom by substitutions, deletions or/and insertions of single amino acids or short amino acid sections. The polypeptide is obtainable by expression of the nucleic acid sequence in a suitable expression system (cf. Sambrook et al., supra).

The invention further comprises a cell transformed with a nucleic acid or a vector according to the invention. The cell may be a eukaryotic or a prokaryotic cell, eukaryotic cells being preferred.

The present invention also comprises the use of the polypeptide or fragments thereof as immunogen for the production of antibodies. Standard protocols for obtaining antibodies may be used.

The present invention also comprises a pharmaceutical composition comprising a nucleic acid, modified nucleic acid, vector, cell, polypeptide or antibody as defined herein as active component.

The pharmaceutical composition may comprise pharmaceutically acceptable carriers, vehicles and/or additives and additional active components, if desired. The pharmaceutical composition can be used for diagnostic purposes or for the production of therapeutic agents. Particularly preferred is the use as a therapeutic agent for the modulation of the immune system.

Since the human semaphorin VIa (hsemaVIa) gene is involved in neuronal development and regeneration mechanisms during apoptosis, this gene can be used to design drug target structures. Members of the semaphorin gene family act as guidance signals and regulatory molecules during neuronal development. Besides its role in development, semaphorin has essential functions in the immune system. Semaphorin can also be linked to potential cancer, drug resistance and disease genes.

On the basis of a phylogenetic approach, the semaphorin gene family is currently distinguished into eight classes containing invertebrate (classes I, II) and vertebrate proteins (classes III-VIII). Consistent with this nomenclature, the newly identified semaphorin is grouped into class VI as human semaphorin VIa.

RNA expression studies have revealed hsemaVIa expression in areas consistent with a role of hsemaVIa as a guidance and regulatory signal during development and regeneration. Specialized domains in the cytoplasmic tail of the hsemaVIa gene product containing cytoskeletal binding elements show that hsemaVIa is also involved in differentiation, cytoskeletal stabilization and plasticity.

Finally, the invention is also directed to the use of the herein described pharmaceutical compositions for effecting differentiation, cytoskeletal stabilization and/or plasticity.

The invention is further described by Figure 1 which shows SEQ ID NO:1, the coding nucleotide sequence of the human semaphorin VIa gene.

Claims

1. Nucleic acid coding for human semaphorin VIa comprising:
   (a) the nucleotide sequence shown in SEQ ID NO:1,
   (b) a sequence corresponding to the nucleotide sequence shown in SEQ ID NO:1 within the degeneration of the genetic code, or
   (c) a sequence which hybridizes with the sequences of (a) or/and (b) under stringent conditions.

2. Nucleic acid according to claim 1, characterized in that it has a homology greater than 80% to the nucleotide sequence of SEQ ID NO:1.

3. Modified nucleic acid or nucleic acid analog having a nucleotide sequence according to claim 1 or 2, or a section having at least 12 bases therefrom.

4. A nucleic acid which encodes a protein having a semaphorin domain and which hybridizes under stringent conditions to a nucleic acid comprising the nucleotide sequence shown in SEQ ID NO:1.

5. Nucleic acid according to any of the preceding claims, which encodes a protein inhibiting neurite outgrowth.

6. Nucleic acid according to claim 5, which encodes a protein inhibiting neurite outgrowth of CNS-neuron.

7. Recombinant vector, characterized in that it contains at least one copy of a nucleic acid according to claims 1-6, or a section therefrom.

8. Vector according to claim 4,
characterized in that it is a eukaryotic vector.

9. Cell,
characterized in that it is transformed with a nucleic acid according to any of claims 1-6 or with a vector according to claim 7 or 8.

10. Polypeptide encoded by a nucleic acid according to claims 1-6.

11. Use of the polypeptide according to claim 10 or of fragments of said polypeptide as immunogen for the production of antibodies.

12. Antibodies against a polypeptide according to claim 10.

13. Pharmaceutical composition comprising:
(a) a nucleic acid according to any of claims 1-6,
(b) a recombinant vector according to claim 7 or 8,
(c) a cell according to claim 9,
(d) a polypeptide according to claim 10, or/and
(e) an antibody according to claim 12.

14. Use of a peptide according to claim 10 for the preparation of a pharmaceutical composition.

15. Use of a composition according to claim 13 as diagnostic agent.

16. Use of a composition according to claim 13 for the production of a therapeutic agent.

17. Use according to claim 16 for the modulation of the immune system.

18. Use according to any of claims 15-17 in gene therapy.

19. Use according to any of claims 15-18 for effecting differentiation, cytoskeletal stabilization and/or plasticity.

Abstract

Human semaphorin VIa, a novel gene involved in neuronal development and regeneration mechanisms, is described.

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